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| 09/855,797 | 05/16/2001 | James L. Hartley | 0942.285000G | 2106 |

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| EXAMINER | |
|---|---|
| SCHLAPKOHL, WALTER | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/855,797 | HARTLEY ET AL. | |
| | Examiner | Art Unit | |
| | Walter Schlapkohl | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on 7/20/2005.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 52-59 and 61-78 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 52-59 and 61-78 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



SUD

**DETAILED ACTION**

Receipt is acknowledged of amendments to claims 52, 57-59, 61-65, 69-72, 74-76 and 78 in the papers filed on 7/20/2005. Claims 52-59 and 61-78 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections - 35 USC § 112***

Claims 52-59 and 61-78 were rejected in the papers filed 4/20/2005 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is withdrawn due to Applicant's amendment. Any response to arguments made to this rejection in the papers filed 7/20/2005 is thus rendered moot.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 52-59, 61-63 and 66-78 were rejected under 35 U.S.C. 102(b) as being anticipated by Bebee et al (U.S. Patent No. 5,434,066). This rejection is withdrawn due to Applicant's amendment and has been replaced with a new rejection under the same statute as necessitated by Applicant's amendment.

Claims 52-58, 62, and 66-68 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyd (Boyd, A.C. Nucleic Acids Research **21**(4):817-821, 1993). **This is a new rejection necessitated by Applicant's amendment file 7/20/2005.**

Regarding claims 52-58, 62 and 66-68, Boyd teaches an *in vitro* method for synthesizing one or more nucleic acid molecules comprising one or more site-specific recombination sites by combining blunt-ended DNA fragments (isolated linear nucleic acid molecules) with linearized vectors that contain lox recombination sites. The linearized vectors are ligated *in vitro* to the blunt-ended DNA fragments (linear nucleic acid molecule). At this stage the linearized vectors themselves act as the adapters. The ligated blunt-ended fragments and linearized vectors are then recombined *in vitro* by the site-

specific recombinase, Cre (see the entire document, especially page 818 and Figure 2).

Regarding claim 53, Boyd teaches that fragments were obtained from amplification of inter-Alu region of total genomic DNA from a hybrid cell line B2.13 (page 818).

Regarding claims 54-55, Boyd teaches that the blunt-ended fragments could be produced by PCR amplification or by cDNA synthesis (see page 817, column one and page 821, second paragraph).

Regarding claim 56, on page 817 Boyd teaches alternative methods involving fragment ends rendered cohesive by linker sequences (equivalent to digestion by restriction endonucleases).

Regarding claims 57-58, Boyd teaches that the ligated vectors are added to both termini of the linear nucleic acid molecule (see especially page 818, second column, last paragraph and Figure 2). The vectors which have been added are comprised of lox sites which are inverted repeats, i.e. different from each other.

Regarding claim 62, Boyd teaches that the recombination sites are lox recombination sites (see Figure 2).

Regarding claims 66-68, Boyd teaches that the Cre-induced recombination results in the production of a vector comprising

the linear nucleic acid molecule, wherein at least one linear nucleic acid molecule is a population of nucleic acid molecules (Alu-PCR products amplified from genomic DNA - see page 818, paragraph bridging first and second columns; page 819, second paragraph).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35

U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**This is a new rejection necessitated by Applicant's amendment filed 7/20/2005.**

Claims 61-65 and 69-72, 74-76, and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyd (Nucleic Acids Research **21**(4):817-821, 1993) in view of Alonso et al (FEMS Microbiology Letters 142:1-10).

Boyd teaches an *in vitro* method for synthesizing one or more nucleic acid molecules comprising one or more site-specific recombination sites by combining blunt-ended DNA fragments (isolated linear nucleic acid molecules) with linearized vectors that contain lox recombination sites. The linearized vectors are ligated *in vitro* to the blunt-ended DNA fragments (linear nucleic acid molecule). At this stage the linearized vectors themselves act as the adapters. The ligated blunt-ended fragments and linearized vectors are then recombined at lox sites *in vitro* by Cre recombinase (see the entire document, especially page 818 and Figure 2).

Boyd does not teach this procedure for two or more site-specific recombination sites that do not substantially recombine with each other or for recombinases Int, IHF, Xis and Fis.

Alonso et al teach *in vitro* site-specific recombination for two or more site-specific recombination sites that do not substantially recombine with each other (lambdoid attB, attP, attL and attR) and for recombinases Int, IHF, and Xis and Fis.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute *in vitro* recombination performed by Int, IHF, Xis or Fis as taught by Alonso et al in the method of synthesizing one or more nucleic acid molecules as taught by Boyd because Alonso teaches that it is within the skill of the art to utilize Int family recombinases to recombine DNA *in vitro* either between site-specific locations on the same DNA molecule (resolution and inversion) or on different molecules (integration)depending upon the choice of recombination sites and recombination proteins used and Boyd teaches that it is within the skill of the art to synthesize one or more nucleic acid molecules comprising one or more site-specific recombination sites utilizing an Int family recombinase, Cre, which recognizes and recombines DNA at site-specific recombination (lox) sites.

One would have been motivated to substitute one or more recombination sites that don't recombine with each other and the appropriate recombinases for the expected benefit of directing excisive or integrative recombination (or both in sequence) as

taught by Alonso et al. For example, the Int protein cuts and reseals DNA to carry out strand exchange, whereas the Xis protein is required only for excisive recombination (Alonso et al, page 2 first paragraph).

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when utilizing a different Int family recombinase and its corresponding site-specific recombination site (as taught by Alonso et al) in Boyd's method of synthesizing one or more nucleic acid molecules comprising one or more site-specific recombination sites.

Claims 59, 61-62, 71-73, 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyd (Nucleic Acids Research **21**(4):817-821, 1993) in view of Waterhouse et al (Nucleic Acids Research 21(9):2265-2266). **This is a new rejection necessitated by Applicant's amendment filed 7/20/2005.**

Boyd teaches an *in vitro* method for synthesizing one or more nucleic acid molecules comprising one or more site-specific recombination sites by combining blunt-ended DNA fragments (isolated linear nucleic acid molecules) with linearized vectors that contain lox recombination sites. The linearized vectors

are ligated *in vitro* to the blunt-ended DNA fragments (linear nucleic acid molecule). At this stage the linearized vectors themselves act as the adapters. The ligated blunt-ended fragments and linearized vectors are then recombined at lox sites *in vitro* by Cre recombinase (see the entire document, especially page 818 and Figure 2).

Boyd does not teach this method for lox site-specific recombination sites or portions thereof that do not substantially recombine with each other.

Waterhouse et al teach site-specific recombination at loxP and loxP511 site-specific recombination sites that do not substantially recombine with each other within the same vector. Utilizing these loxP/loxP511 site-specific recombination sites, Waterhouse et al avoid deletion of VH genes and instead create chimeric vectors which can be resolved to generate their original vectors as well as two new vectors with desired gene segments (Waterhouse et al, page 2265, 3rd paragraph and page 2266, Figure 1).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute loxP/loxP511 sites as taught by Waterhouse et al in the method of synthesizing one or more nucleic acid molecules as taught by Boyd because Waterhouse teaches that it is within the skill of

the art to utilize a wild-type loxP site and a mutated loxP site (loxP511) within the same vector and Boyd teaches that it is within the skill of the art to synthesize one or more nucleic acid molecules comprising one or more site-specific recombination sites utilizing Cre recombinase and loxP site-specific recombination sites.

One would have been motivated to substitute the wild-type loxP sites of Boyd with the loxP/loxP511 sites of Waterhouse et al for the expected benefit of restricting recombination reactions to occurring at sites of matching sequence within different vectors only, thereby avoiding deletion of desired DNA segments. For example, Waterhouse et al avoid deletion of VH genes and instead create chimeric vectors which can be resolved to generate the original vectors as well as two new vectors with desired gene segments (Waterhouse et al, page 2265, 3rd paragraph and page 2266, Figure 1).

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when utilizing the loxP/loxP511 site-specific recombination sites as taught by Waterhouse et al in Boyd's method of synthesizing one or more nucleic acid molecules

comprising the use of the Cre/lox system with one or more site-specific recombination sites.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy

should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter A. Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday

through Friday from 8:30 AM to 5:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office.)

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

**Walter A. Schlapkohl, Ph.D.**
**Patent Examiner**
**Art Unit 1636**

September 30, 2005

TERRY MCKELVEY
PRIMARY EXAMINER